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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference			FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)			
N.74368A DMG/IJB				- 1701111110		
International application No.			International filing date (day/mo	nth/year)	Priority date (day/month/year)	
PCT/GB9			18/03/1999		20/03/1998	
International C12N15/		ent Classification (IPC) or na	ational classification and IPC			
0121113/	55					
Applicant						
ST. GEO	RGE	'S HOSPITAL MEDIC	AL SCHOOL et al.			
1. This i	nterna	ational preliminary exam	ination report has been prepa	red by this In	ternational Preliminary Examining Authority	
		smitted to the applicant a		· · · · · · · · · · · · · · · · · · ·	, ,	
2. This f	REPO	RT consists of a total of	6 sheets, including this cove	r sheet.		
□ T	his re	port is also accompanie	d by ANNEXES, i.e. sheets of	the descripti	ion, claims and/or drawings which have rectifications made before this Authority	
(s	een a see R	lmended and are the bas ule 70.16 and Section 6	of the Administrative Instru	ctions under	the PCT).	
These	ann	exes consist of a total of	sheets.			
3. This r	eport	contains indications rela	ating to the following items:			
· · · · · · · ·						
I	\boxtimes	Basis of the report				
11		Priority				
	×		ppinion with regard to novelty,	inventive ste	p and industrial applicability	
IV	_	Lack of unity of invention	•	to novoltvi ini	vántivo etan or industrial applicability:	
V	×		ons suporting such statement	to novelty, in	ventive step or industrial applicability;	
VI		Certain documents cite				
VII		Certain defects in the in	nternational application			
VIII	\boxtimes	Certain observations of	n the international application			
Date of sub	missio	on of the demand	Date	of completion of	of this report	
05/10/1999			08.0	5.2000		
New				ningal officer		
		g address of the internationa ining authority:	ai Auth	orized officer	Se SHOULS MEETING.	
	Euro	pean Patent Office		_	_ (* a)	
<i><u>)</u>)))</i>)298 Munich +49 89 2399 - 0 Tx: 523656		nen, P	130 mg	
		+49 89 2399 - 0 TX; 52365t	o epina a		TOWN THE COURT OF THE COURT	

I. Basis of the r port

1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.): Description, pages: 1-47 as originally filed Claims, No.: 1-49 as originally filed 2. The amendments have resulted in the cancellation of: ☐ the description, pages: ☐ the claims. Nos.: ☐ the drawings, sheets: 3.

This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)): 4. Additional observations, if necessary: see separate sheet III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of: ☐ the entire international application. ☑ claims Nos. 21-24. because:

the said international application, or the said claims Nos. 21-24 relate to the following subject matter which

does not require an international preliminary examination (specify):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/00849

see	sep	arat	e s	heet
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the description, claims or drawings (<i>indicate particular elements below</i>) or said claims Nos. are so unclear that no meaningful opinion could be formed (<i>specify</i>):
the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes:

Claims 1-36, 38-49

No:

Claims 37

Inventive step (IS)

Yes: Claims 2-5, 7-36, 38-49

No: Claims 1 and 6

Industrial applicability (IA)

Yes:

Claims 1-20, 25-49

No: Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: FR-A-2 682 967 (PASTEUR INSTITUT; UNIV MASSEY (FR)) 30 April 1993 (1993-04-30)

D2: EP-A-0 288 306 (MCFADDEN JOHN JO; TAYLOR JOHN HERMON (GB)) 26 October 1988 (1988-10-26)

D3: CHEMICAL ABSTRACTS, vol. 74, no. 5, 1 February 1971 (1971-02-01) Columbus, Ohio, US; abstract no. 20614, KHACHATURYAN, A. A. ET AL: 'Formation of acylases by hydrocarbon-oxidizing microorganisms' & BIOL. ZH. ARM. (1970), 23(7), 40-7

D4: WO 97/23624 (cited in the application as PCT/GB96/03221)

D5: Australian Veterinary Journal 72 (1995) 458-462

The documents D4-D5 were not cited in the international search report. A copy of D5 has been appended to the first written opinion.

Re Item I

Basis of the opinion

The sequence listings (substitute sheets 1-6; rule 26; published with WO 1. 99/49054) have been taken into account.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

2. For the assessment of the present claims 21-24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 21-24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 3. The present application concerns different aspects of the known pathogen Mycobacterium avium. One aspect is the identification within the genome of the subspecies paratuberculosis (MAP) of a new uninterrupted gene designated mpa (SEQ ID NO:1) coding for a enzyme (SEQ ID NO:2) having an acylase function. Mycobacterium is a known major producer of acylase (see D3). In another aspect, the application refers to newly identifed mycobacterial insertion sequences in interrupted mpa genes of closely related but less pathogenic mycobacteria subspecies silvaticum and TMC724 (ATCC 25291); see page 2 lines 11-14 of the present description. It is therefore considered that these known, less-pathogenic mycobacteria are prejudicial to the novelty of claim 37 on file (Art. 33(2) PCT).
- 4. The prior art has referred already to several genes specific for pathogenic mycobacteria: D4 is an example, disclosing a nucleotide sequence representing a pathogenicity island and D5 referring to a multiplex PCR based on the IS900 insertion sequence specific for M paratuberculosis (see also D1 for IS900 and D2 for insertion sequences in mycobacteria in general).

Although it is known that virulent strains contain special lipids no prior art is available which would suggest to isolate and clone the encoding gene for the particular acylase referred to in the present application. An inventive step is acknowledged for the subject-matter clearly referring to the characterized acylase (referred to in part in claim 2 and depending claims) as well as to the newly found insertion sequences.

5. In view of the fact that acylase from mycobacteria has been described (see D3), it is considered that its purification and cloning of an encoding gene is obvious to the skilled person for the generally claimed subject-matter not characterized by a sequence.

Therefore, the present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claims 1 and 6 does not involve an inventive step (Rule 65(1)(2) PCT).

Re Item VIII

Certain observations on the international application

6. In conjunction with the above observation with respect to the lack of inventive step, it is noted that Article 6 of the PCT requires that all independent claims contain the essential technical feature(s) of the invention (see also Rule 6.3(b) PCT).

At present it is considered that the essential features of the present application relate to the specified mpa gene and its insertions.

7. Claims 2 and 5 refer to polynucleotide comprising a nucleotide capable of hybridising to a fragment of the nucleotide sequence set out in SEQ ID NO:1. The wording hybridising is undefined as it does not have a well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims 2 and 5 and depending claims unclear (Article 6 PCT). The description is also not clear in defining the **minimal** requirement e.g. with respect to % of homology or hybridising conditions.

A similar objection is raised against claims 40 and 42, as well as claim 7 against "a polypeptide substantially homologous thereto".

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



WO 99/49054

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: (11) International Publication Number: C12N 15/55, 15/85, 9/18, C07K 16/40, A1 (43) International Publication Date: 30 September 1999 (30.09.99) C12N 1/20, C12Q 1/68, 1/44, A61K 39/04, 48/00, 38/46 // (C12N 1/20, C12R

(21) International Application Number:

PCT/GB99/00849

(22) International Filing Date:

18 March 1999 (18.03.99)

(30) Priority Data:

9806093.2

20 March 1998 (20.03.98)

GB

(71) Applicant (for all designated States except US): ST. GEORGE'S HOSPITAL MEDICAL SCHOOL [GB/GB]; Cranmer Terrace, London SW17 0RE (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HERMON-TAYLOR, John [GB/GB]; St. George's Hospital Medical School, Dept. of Surgery, Cranmer Terrace, London SW17 0RE (GB). BULL, Timothy, John [GB/GB]; St. George's Hospital Medical School, Dept. of Surgery, Cranmer Terrace, London SW17 ORE (GB).

(74) Agent: GOLDIN, Douglas, Michael; J.A. Kemp & Co., 14 South Square, Grays Inn, London WC1R 5LX (GB).

(81) Designated States: AU, CA, JP, NZ, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

amendments.

With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of

(54) Title: DIAGNOSTICS AND VACCINES FOR MYCOBACTERIAL INFECTIONS OF ANIMALS AND HUMANS

(57) Abstract

This invention relates to the protein, Mycobacterium paratuberculosis acylase (mpa) and the gene encoding mpa, which we have identified in the pathogen Mycobacterium paratuberculosis Mptb (also designated Mycobacterium avium subspecies paratuberculosis MAP), and to their use in the diagnosis of Mptb/MAP infections in animals and humans, as well as their use as components of vaccines for the prevention and treatment of diseases caused by Mptb/MAP. The importance of an intact uninterrupted mpa gene as a determinant of pathogenicity in Mptb/MAP is recognised and the invention also provides attenuated strains of normally pathogenic Mptb/MAP and other mycobacteria in which mpa has been inactivated, for use as vaccines.

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Inte ional Application No. PCT/GB 99/00849 A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/55 C12N15/85 C12N9/18 C07K16/40 C12N1/20 C12Q1/68 C12Q1/44A61K39/04 A61K48/00 A61K38/46 //(C12N1/20,C12R1:32) According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C12N C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 682 967 A (PASTEUR INSTITUT ;UNIV MASSEY (FR)) 30 April 1993 (1993-04-30) claims	1
A	EP 0 288 306 A (MCFADDEN JOHN JO ;TAYLOR JOHN HERMON (GB)) 26 October 1988 (1988-10-26) claims	1

X Further documents are listed in the continuation of box C.	X Patent family members are listed in annex.		
 Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filling date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filling date but later than the pnority date claimed 	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 16 July 1999	Date of mailing of the international search report 30/07/1999		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Delanghe, L		

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Inte :onal Application No PCT/GB 99/00849

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C.(Continu	Citation of document, with indication where generalities of the relevant		Polovost to plains Mr.
- Lutagory	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 74, no. 5, 1 February 1971 (1971-02-01) Columbus, Ohio, US; abstract no. 20614, KHACHATURYAN, A. A. ET AL: "Formation of acylases by hydrocarbon-oxidizing microorganisms" XP002109388 abstract & BIOL. ZH. ARM. (1970), 23(7), 40-7,		1

2

....ernational application No.

PCT/GB 99/00849

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first she t)
This Inte	mational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claim(s) 21 - 24 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inter	national Searching Authority found multiple inventions in this international application, as follows:
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark o	The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

information on patent family members

Inter onal Application No PCT/GB 99/00849

Patent do cited in sea			Publication date		atent family member(s)	Publication date
FR 2682	967	Α	30-04-1993	WO	9308284 A	29-04-1993
				EP	0666917 A	16-08-1995
				JP	7504082 T	11-05-1995
				NZ	244901 A	26-07-1995
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				DE	3854767 T	05-09-1996
				DK	524289 A	22-12-1989
				EΡ	0356450 A	07-03-1990
				WO	8808456 A	03-11-1988
				JР	3503837 T	29-08-1991
				US	5225324 A	06-07-1993

HATENT COOPERATION TREATY

To:

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Assistant Commissioner for Patents United States Patent and Trademark Office

Box PCT

Washington, D.C.20231 ÉTATS-UNIS D'AMÉRIQUE

Applicant's or agent's file reference

Date of mailing (d	ay/month/year)
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15 November 1999 (15.11.99)

in its capacity as elected Office

International application No. PCT/GB99/00849

International filing date (day/month/year)
18 March 1999 (18.03.99)

N74368A DMG

Priority date (day/month/year)
20 March 1998 (20.03.98)

Applicant

HERMON-TAYLOR, John et al

1.	The designated Office is hereby notified of its election made:
	X in the demand filed with the International Preliminary Examining Authority on:
	05 October 1999 (05.10.99)
	in a notice effecting later election filed with the International Bureau on:
	- · · · · · · · · · · · · · · · · · · ·
2.	The election X was was not
	made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).
l	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35



(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference						
N74368A DMG	ACTION (Form PCT/ISA/220) as well as, where applicable, item 5 below.					
International application No.	application No. International filing date (day/month/year) (Earliest) Priority Date (day/month/year)					
PCT/GB 99/00849	18/03/1999 20/03/1998					
Applicant						
ST. GEORGE'S HOSPITAL MEDI	ICAL SCHOOL et al.					
This International Search Report has been according to Article 18. A copy is being tra	n prepared by this International Searching Auth ansmitted to the International Bureau.	nority and is transmitted to the applicant				
according to riticity for recept to being the	Illimited to the international bureau.					
This International Search Report consists						
X It is also accompanied by	a copy of each prior art document cited in this	report.				
Basis of the report		-				
a. With regard to the language, the i	international search was carried out on the bas	sis of the international application in the				
	ess otherwise indicated under this item.					
the international search wa Authority (Rule 23.1(b)).	as carried out on the basis of a translation of the	ne international application furnished to this				
b. With regard to any nucleotide and was carried out on the basis of the	d/or amino acid sequence disclosed in the in	temational application, the international search				
	e sequence listing : nal application in written form.					
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	this Authority in computer readble form.					
the statement that the sub- international application as	sequently furnished written sequence listing do s filed has been furnished.	oes not go beyond the disclosure in the				
X the statement that the informished	rmation recorded in computer readable form is	s identical to the written sequence listing has been				
2. X Certain claims were foun	nd unsearchable (See Box I).					
3. Unity of invention is lack	•					
A APPAR OF THE RESIDENCE AND THE STATE OF TH						
 With regard to the title, the text is approved as subsequents. 	hmittad hu the engligant					
	the text is approved as submitted by the applicant. the text has been established by this Authority to read as follows:					
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- 2200						
5. With regard to the abstract,						
the text is approved as submitted by the applicant. the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may,						
within one month from the	date of mailing of this international search repo	ort, submit comments to this Authority.				
6. The figure of the drawings to be publis						
as suggested by the applic						
	plicant failed to suggest a figure. Just better characterizes the invention.					
Decense una ligure petter c	maracterizes the invention.					



International application No.

PCT/GB 99/00849

Box I Observations where certain claims were f und unsearchable (Continuation of item 1 of first sheet)
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Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

ternational Application No CT/GB 99/00849

C12N1/20

A61K38/46

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/55 C12N15/85 C12N9/18 C07K16/40
C12Q1/68 C12Q1/44 A61K39/04 A61K48/00
//(C12N1/20,C12R1:32)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 $\begin{array}{ll} \mbox{Minimum documentation searched (classification system followed by classification symbols)} \\ \mbox{IPC 6} & \mbox{C12N} & \mbox{C07K} \end{array}$

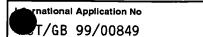
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUM	ENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Α	FR 2 682 967 A (PASTEUR INSTITUT ;UNIV MASSEY (FR)) 30 April 1993 (1993-04-30) claims	1
A	EP 0 288 306 A (MCFADDEN JOHN JO; TAYLOR JOHN HERMON (GB)) 26 October 1988 (1988-10-26) claims/	

Further documents are listed in the continuation of box C.	χ Patent family members are listed in annex.		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report		
16 July 1999	30/07/1999		
Name and mailing address of the ISA	Authorized officer		
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Delanghe, L		

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ernational Application No CT/GB 99/00849

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(57) Abstract

The invention provides a nucleotide sequence representing a pathogenicity island found in species of pathogenic mycobacteria. The islands are shown as SEQ ID NOs: 3 and 4 and comprises several open reading frames encoding polypeptides. These polypeptides and their use in diagnosis and therapy form a further aspect of the invention.

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